PROPOFOL DECREASES RANDOM AND CHEMOTACTIC STIMULATED LOCOMOTION OF HUMAN NEUTROPHILS IN VITRO

A. G. JENSEN, C. DAHLGREN AND C. EINTREI

SUMMARY

We have studied the influence of clinical concentrations of propofol (2,6-diisopropylphenol), emulsified propofol (Diprivan) and the emulsifier of propofol (Intralipid 10%) on random and chemotactic locomotion of human polymorphonuclear leucocytes in an agarose assay. Random locomotion was decreased (P < 0.001) to a similar extent by the three drugs. Concentrations of propofol 2.5 μg ml⁻¹ and greater, and of Diprivan 3.33 μg ml⁻¹ and greater, also reduced chemotaxis (P < 0.05) against both zymosan-activated human serum (C5a) and N-formyl-methionyl-leucyl-phenylalanine (FMLP), used as chemoattractants. Intralipid reduced chemotaxis towards C5a but not towards FMLP. We conclude that propofol in clinically relevant concentrations may adversely affect leucocyte locomotion in vitro. (Br. J. Anaesth. 1993; 70: 99-100)

KEY WORDS


METHODS AND RESULTS

Venous blood was obtained from 15 healthy adult volunteers and neutrophils were separated from heparinized blood using standard techniques [2]. Agarose (Litex, Copenhagen, Denmark) was dissolved in 60 ml of water by heating (1.2% w/v). After temperature equilibration, equal volumes of the agarose solution and of double-concentrated Geys medium and 2% human serum albumin were mixed. This solution was supplemented and mixed with the drug under investigation and poured into tissue culture dishes (60 x 13 mm; Flow, Edinburgh, Scotland). Twelve holes were cut in the agarose using a specially constructed mould. After addition of 10 μl of normal human serum containing zymosan (C5a) 5 mg ml⁻¹ to two of the holes in each plate, the plates were incubated for 1 h at 37 °C in 5% carbon dioxide. Ten microlitre of the cells was added to the six holes in the centre of the plate and 10 μl of N-formyl-methionyl-leucyl-phenylalanine (FMLP) 10⁻⁷ mol litre⁻¹ was added to two of the holes at the periphery. The plates were then incubated for 60 min under the same conditions as before. The cells were fixed in 3.7% cold formalin, and stained with Giemsa.

The migration distance was measured under a microscope, measuring on an arbitrary scale the distance from the edge of the well to the leading front of neutrophils [3]. The mean and SD of at least 12 readings were calculated for each concentration and drug. The significance of the difference in migration in arbitrary scale units between the control cells and the cells treated with different drugs and different concentrations was assessed by Student's t test. P < 0.05 was considered significant.

The effects on granulocyte locomotion of four different concentrations of Diprivan were studied: 1.66 μg ml⁻¹, 2.5 μg ml⁻¹, 3.33 μg ml⁻¹ and 33.3 μg ml⁻¹. Random locomotion was reduced significantly by Diprivan—by about 50% for all the concentrations used. Directional locomotion towards

ANDERS GADEGAARD JENSEN, MD., D.E.A.A.; CHRISTINA EINTREI, M.D., PH.D.; Department of Anaesthesiology, Faculty of Health Sciences, Linköping University Hospital, S-581 85 Linköping, Sweden. CLAES DAHLGREN, PH.D., Department of Medical Microbiology and Immunology, University of Göteborg, S-413 46 Göteborg, Sweden. Accepted for Publication: August 18, 1992.

Correspondence to A. G. J.
migration = distance of random migration in controls without (concentrations of Intralipid 10 times greater than noted). 100% tractions of Diprivan (•) propofol (○) and Intralipid (□)

1. Mean locomotion of leucocytes at random and after FIG. (SD)

0.001—compared with respective migration at concentration 0; ***P < **P < 0.05, 0.01 and drug. Significant differences: *P <

of random locomotion was more pronounced than and 33.3 ug ml”

Diprivan 3.33 ug ml” 1

with Diprivan, as random locomotion was reduced the reduction observed after chemoattractants (fig. 1).

1.66 2.5 3.33

2.5 ug ml” was used as chemoattractant (fig. 1). Directional

similar degree as that with Diprivan (fig. 1).

Intralipid did not reduce the migration when FMLP 

gration of the human neutrophil granulocyte. As the relevant concentrations of Diprivan depressed mi-

The major findings of this study were that clinically relevant concentrations of Diprivan depressed migration of the human neutrophil granulocyte. As the reduction was comparable with Diprivan, propofol and Intralipid for random migration and directed migration towards C5a, we conclude that both the drug propofol per se and the emulsifier with a composition similar to that of Intralipid were responsible for the influence on the granulocytes. These effects were neither additive nor concentration-dependent. The depressed migration ability of granulocytes after Intralipid incubation in our study was comparable to the results obtained in a previous study [1] in which an E. coli culture filtrate was used as chemotactic agent. With the design of our study we were not able to determine whether or not the impairment was reversible after discontinuation of the anesthetic, and the clinical significance of this inhibition has not yet been determined. However, any impairment of the responsiveness of the leucocyte is likely to increase the incidence of infection. The Leucocyte Adhesion Deficiency, in which defects in neutrophil chemotaxis and phagocytosis lead to widespread bacterial infections, is an example of such an impairment [4].

Leucocytes have been shown to engulf Intralipid, resulting in reduction in important cell membrane constituents and impaired locomotion [1]. The mechanism by which propofol interferes with the locomotor process is not known but, as propofol is lipid soluble, the depressing effect of this agent on random locomotion could also be mediated by membrane changes induced by the drug. Also, the compounds used in this study could possibly exert their effect on migration by disruption of the contractile system.

Specific receptors for C5a and for FMLP on the surface of neutrophils have been demonstrated, and their recycling patterns are different, as are the basic mechanisms for recognition of chemotactic gradients [5]. This could possibly explain the different results found using these two chemoattractants. The turnover of receptors, and the ability to detect a surface bound gradient, may be disturbed by lipid soluble molecules that can be inserted into lipid membranes. The degree of depression of chemotactic locomotion observed with inhalation anaesthetic agents parallels their lipid solubilities [6] and we suggest that propofol could depress locomotion of leucocytes by the same mechanisms as the inhalation anaesthetics.

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REFERENCES


